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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/054,647	01/22/2002	Robert Lawton	00-1278-C	9151

20306 7590 11/10/2004

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EXAMINER

FORD, VANESSA L

ART UNIT PAPER NUMBER

1645

DATE MAILED: 11/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No. 10/054,647	Applicant(s) LAWTON ET AL.	
	Examiner Vanessa L. Ford	Art Unit 1645	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 16 July 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

- a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.
- b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
- ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on 23 August 2004. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.
2. ☐ The proposed amendment(s) will not be entered because:
- (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);
 - (b) ☐ they raise the issue of new matter (see Note below);
 - (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
 - (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____

3. ☒ Applicant's reply has overcome the following rejection(s): Rejection of claims 1-13 under 35 U.S.C. 112, second paragraph.
4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
5. ☒ The a) ☐ affidavit, b) ☐ exhibit, or c) ☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: see advisory attachment.
6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.
7. ☒ For purposes of Appeal, the proposed amendment(s) a) ☐ will not be entered or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: NONE

Claim(s) objected to: NONE

Claim(s) rejected: 1-13

Claim(s) withdrawn from consideration: _____

8. ☐ The drawing correction filed on _____ is a) ☐ approved or b) ☐ disapproved by the Examiner.
9. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
10. ☒ Other: Advisory attachment.

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Advisory Action Attachment

1. This action is responsive to Applicant's response filed July 16, 2004 is acknowledged.

Rejection Withdrawn

2. In view of Applicant's response the rejection of claims 1-13 under 35 U.S.C. 112, second paragraph is withdrawn, page 12, paragraph 7 of the Final Office action.

Rejections Maintained

3. The rejection of claims 1-13 under 35 U.S.C. 112, first paragraph is maintained for the reasons set forth on pages 3-6, paragraph 4 of the Final Office Action.

The rejection was on the grounds that the claims are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. *This is a written description rejection.*

The specification broadly describes as a part of the invention a composition and an article of manufacture comprising the isolated polypeptide of SEQ ID No: 2 and variants thereof. The specification states "variants in which amino acids of the polypeptides of the invention are substituted, deleted or added in any combination are contemplated by the invention". The specification also states, "that naturally occurring variants and non-naturally occurring variants are included in the invention and may be produced by mutagenesis techniques or by direct synthesis" (page 7). Applicant has broadly described the invention as embracing any substitution, insertion or deletion change of amino acids throughout the length of the polypeptide sequence. Variants of SEQ ID No:2 correspond to sequences from other species, mutated sequences, allelic variants, splice variants, sequences that have a variant degree of identity (similarity, homology), and so forth. None of these sequences meet the written description provision of 35 U.S.C. 112, first, paragraph. The specification

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provides insufficient written description to support the genus encompassed by the claim. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of SEQ ID NO:2, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptide regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Therefore, only SEQ ID NO: 2 but not the full breadth of the claim (or none of the sequences encompassed by the claim) meets the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Applicant urges that written description requires that one skilled in the art must recognize that the Applicant was in possession of the claimed genus, that is, variants of SEQ ID NO:2. Applicant refers to the Guidelines for Examination of Patent Applications under 35 U.S.C. 112, 66 Fed. Reg. 1099, 1106 (2001). Applicant urges that the description of a representative number of species does not require the description to be such specificity that it would provide individual support for each species that the genus embraces. Applicant urges that one species can adequately support a genus. Applicant urges that distinguishing characteristics of a claimed genus include A) partial structure, B) physical and/or chemical properties, C) functional characteristics, D) known or disclosed

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correlation between structure and function, E) method of making and F) combinations of A-E. Applicant urges that the partial structure of the claimed variants are known, i.e. sequences having at least 85 % identity to SEQ ID NO:2 and therefore the variants have about 17 amino acids in common with the 20 amino acid long sequence as set forth in SEQ ID NO:2. Applicant urges that the specification teaches that amino acid substitution variants of the invention can be made. Applicant urges that the specification provides detailed guidance on how to construct variants of SEQ ID NO:2. Applicant urges that the partial structure of the claimed variants are known, (i.e. sequence that have at least 85% identity to SEQ ID NO:2) and therefore, the variants have about 17 amino acids in common with the 20 amino acid long sequence as set forth in SEQ ID NO:2. Applicant urges that physical properties and functional characteristics of the variants are known. Applicant urges that the specification teaches that the polypeptides of the invention "specifically bind to anti-*Ehrlichia* antibodies".

Applicant's arguments filed July 16, 2004 have been fully considered but they are not persuasive. It is the Examiner's position that there is nothing on the record to show that the specification provides adequate written description for the full scope of the claims and therefore does not meet the written description requirement as set forth in 35 U.S.C. 112, first paragraph. Applicant has not shown that they were in possession of variants of SEQ ID No:2 at the time of filing. The specification discloses only species SEQ ID NO: 2 within the genus of the claimed invention. The specification does not provide adequate written description for the full scope of the claimed invention. Applicant has provided no

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structural description accompanying the variant language (i.e. "substitution variants") recited in the claims. While use of BLAST and other sequence comparison tools are known, it is not routine in the art to screen for multiple substitutions or multiple modifications of other types and the positions within the polypeptide's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity are limited in any protein and the result of such modifications is unpredictable based on the instant disclosure. However, the claims are directed to a composition of matter and an article of manufacture comprising an isolated polypeptide consisting essentially of SEQ ID NO:2 or phenotypically silent amino acid substitution variant thereof that specifically binds to an anti-*Ehrlichia* antibodies which encompasses sequences from other species, mutated sequences, splice variants, sequences that have a recited degree of identity (similarity, homology), and so forth. The general knowledge of the art concerning species does not provide any indication of how the structure of a limited number of other species is representative of unknown species. Applicant refers to Table 1 of the instant specification and Applicant asserts that "the partial structure of the claimed variants are known, i.e. sequence that have at least 85% identity to SEQ ID NO:2 and therefore, the variants have about 17 amino acids in common with the 20 amino acid long SEQ ID NO:2". It should be noted that Table 1 of the specification discloses candidate sequences that have sequence identity to SEQ ID NO:2 identified by sequence comparison algorithms. Applicant asserts that "methods of making variants of SEQ ID NO:2 are well-known in the art and are described in the specification".

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Applicant is asked to point out page and line number in the specification where actual phenotypically silent amino acid substitution variants of SEQ ID NO: 2 are disclosed. It should be remembered that the requirement under the U.S.C. 35 112, first written description is that Applicant is possession of the claimed invention not in possession of a method of making the claimed invention. What amino acids are modified and at which positions are these modifications made? Where does the specification disclose an actual phenotypically silent amino acid substitution variant of SEQ ID NO: 2, that binds to an anti-*Ehrlichia* antibody (as recited in the claims)? It should be remembered that the claims are drawn to products (i.e. a composition of matter and an article of manufacture) not methods. One skilled in the art would conclude that Applicants were not in possession of the claimed genus polypeptides by the information disclosed in the specification.

4. The rejection under 35 U.S.C. 112, first paragraph is maintained for 1-13 for the reasons set forth pages 6-9, paragraph 5 of the Final Office Action.

The rejection was on the grounds that the claims rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition and an article of manufacture that comprise SEQ ID No:2, does not reasonably provide enablement for a composition or an article of manufacture that comprise variants of SEQ ID. No:2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-6 are directed to a composition and a article of manufacture comprising the isolated polypeptides of SEQ ID NO: 2 and variants thereof.

The specification is enabling only for the polypeptides of SEQ ID NO:2 as disclosed in the specification. The specification states that "variants in which amino acids of the polypeptides of the invention are substituted, deleted or added in any combination are contemplated by the invention". The specification also

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states " that naturally occurring variants and non-naturally occurring variants are included in the invention and may be produced by mutagenesis techniques or by direct synthesis" (page 7). The specification teaches that there are many tolerable and conservative amino acid substitutions which can be made that are not critical to protein function (pages 7-9). There is no guidance provided as to which amino acids can be added, deleted or substituted and the polypeptide would retain its biological function. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Since the amino acid sequence of the polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar activity/utility requires a knowledge with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expected intolerant to modification) and detailed knowledge of the ways in which the polypeptide's structure relates to function. However, the problem of the prediction of polypeptide structure from mere sequence data of a single polypeptide and in turn utilizing predicted structural determinations to ascertain functional aspects of the polypeptide and finally what changes can be tolerated with respect thereto is extremely complex and outside of the realm of routine experimentation.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen multiple substitutions or multiple modifications of other types and the positions within the polypeptide's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity are limited in any polypeptide and the result of such modifications is unpredictable based on the instant disclosure. One skilled in the art would expect any tolerance to modifications, e.g., multiple substitutions. The sequence of some polypeptides is highly conserved and one skilled in the art would not expect tolerance to any amino acid modification in such polypeptides.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to selecting other antigens having claimed functional features, 3) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level). One of skill in the art would require guidance, in order to make or use polypeptides that are

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variants of SEQ ID NO: 2 in a manner reasonable in correlation with the scope of the claims. Without proper guidance, the experimentation is undue.

Applicant urges that a structural description of the claimed variants is provided by the specification. Applicant urges that variants are amino acid substitution variants that have at least 85 % identity to SEQ ID NO:2 and specifically bind an anti-*Ehrlichia* antibody. Applicant urges that the partial structure of the claimed variants are known, i.e. sequences having at least 85 % identity to SEQ ID NO:2 and therefore the variants have about 17 amino acids in common with the 20 amino acid long SEQ ID NO:2 and specifically bind an anti-*Ehrlichia* antibody. Applicant refers to Table 1 and urges that the specification provides structural guidance as to which amino acids can be changed and the variant polypeptides retain their biological function. Applicant urges that the standard for enablement is whether one reasonable skilled in the art could make and use the invention for the disclosures in the patent coupled with information known in the art without undue experimentation. Applicant urges that the claims are enabled by the instant specification.

Applicant's arguments filed July 16, 2004 have been fully considered but they are not persuasive. It is the Examiner's position that Applicant has not shown enablement for variants of SEQ ID No.2. Applicant has not disclosed what amino acids are modified and at which positions are these modifications made to arrive at phenotypically silent substitution variants as set forth in the claims. Where does the specification disclose an actual phenotypically silent

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amino acid substitution variant of SEQ ID NO: 2, that binds to an anti-*Ehrlichia* antibody (as recited in the claims)? The specification discloses only species SEQ ID NO 2 within the genus of the claimed invention. The specification fails to provide guidance as to which amino acids can be changed and the polypeptides still retain their claimed biological function. In the present state of the art, the structure of a limited number of species does not provide guidance to the structure of others and is insufficient to support the claimed invention. To address Applicant's comment regarding the requirements as set forth under 35 U.S.C. 112, first paragraph, it should be noted that the 35 U.S.C. 112 first paragraph requires that Applicants teach how to "make and use" the claimed invention not how to "find" variants of SEQ ID NO:2 that specifically bind to an anti-*Ehrlichia* antibody". Applicant is asked to direct the Examiner to an actual structural description of phenotypically silent substitution variants of SEQ ID NO:2 in the specification as indicated by the claims. Applicant has not disclosed in the instant specification what amino acids at which positions in SEQ ID NO:2 are substituted? One skilled in the art would require guidance in order to make and use the claimed composition of matter or article of manufacture comprising phenotypically silent amino acid substitution variants of SEQ ID NO:2 commensurate in scope with the claims. Therefore, one skilled in the art would have to be successful in producing polypeptides that are variants of SEQ ID NO:2 which have a defined structure to satisfy the enablement requirement under 35 U.S.C. 112, first paragraph.

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5. The rejection of claims 1-13 under 35 U.S.C. 102(b) is maintained for the reasons set forth on pages 9-11, paragraph 6 of the previous Final Action.

The rejection was on the grounds that Rikihisa et al teach immunogenic compositions comprising the isolated polypeptide of SEQ ID NO:2 and pharmaceutically acceptable adjuvants (page 12). Rikihisa et al teach an antigen (i.e. isolated polypeptide) used in a Western immunoblot analysis and a dot blot analysis to detect the presence of antibody to *E. canis* (page 17). The polypeptide of SEQ ID No: 2 is disclosed in Figure 19A). The article of manufacture (i.e. dot blot used in the dot blot analysis) would be inherent in the teachings of the prior art. It is well known in the art to include packing material that comprises a label to indicate the intended use of the article of manufacture. The composition and article of manufacture of Rikihisa, et al appears to be the same as the claimed invention.

Since the Office does not have the facilities for examining and comparing applicant's composition and article of manufacture with the composition and article of manufacture of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the composition and article of manufacture of the prior art does not possess the same material structural and functional characteristics of the claimed composition and article of manufacture). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Applicant urges that Rikihisa et al do not anticipate claims 1-13 because Rikihisa et al do not teach, suggest or inherently disclose each and every element of claims 1-13. Applicant urges that the use of full-length proteins would result in assays that are less sensitive than those disclosed in the instant specification. Applicant urges that the use of whole proteins cannot read on the claimed fragments of the instant invention. Applicant refers to the declaration of Dr. Chandrashekar to support their position.

Applicant's arguments filed July 16, 2004 have been fully considered but they are not persuasive. It is the Examiner's position that there is nothing on the

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record to show that the claimed composition and article of manufacture differs from the composition and article of manufacture of the prior art. The claims are drawn to composition and article of manufacture comprising of an isolated polypeptide consisting essentially of SEQ ID NO:2 and phenotypically silent amino acid substitution variants thereof that specifically bind to an anti-*Ehrlichia* antibody. Rikihisa et al teach an antigen (i.e. isolated polypeptide) used in a Western immunoblot analysis and a dot blot analysis to detect the presence of antibody to *E. canis* (page 17). The claimed invention encompass variants of SEQ ID NO:2, therefore one skilled in the art could reasonably conclude that the polypeptides of the prior art are variants of SEQ ID NO:2 since Rikihisa et al teach that the invention embraces non-naturally occurring allelic forms or derivatives of the outer membrane proteins (i.e. P30) (page 10) and Rikihisa et al teach the isolated polypeptide shown in Figure 21B. Applicant has provided no side-by-side comparison to show that the claimed polypeptide differs from the *E. canis* polypeptides of the prior art. It should be noted that the claims recite "comprising" which is which is open claim language which suggests that other components can be present in the composition or article of manufacture. It should be noted that the claims also recite "consisting essentially of" which is open claim language which suggest that other components (i.e. amino acids) can be present in SEQ ID NO:1 that do not cause a negative effect on the composition or article of manufacture. Therefore, the claims read on the full-length proteins as disclosed by Rikihisa et al. It should be further noted that

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there are not limitations in the claims requiring that the compositions of matter or article of manufacture require any particular level sensitivity. Therefore, the declaration of Dr. Chandrashekar disclosing levels of sensitivity in immunoassays is not relevant. Therefore, Rikihisa et al anticipate the claimed invention.

6. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 308-4242.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (571) 272-0857. The examiner can normally be reached on Monday – Friday from 9:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (571) 272-0864.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov/>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


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October 26, 2004


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